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INVESTIGATION OF NOOTROPIC DRUGS (PYRAMEM AND OROCETAM) FOR THEIR TERATOGENIC EFFECT

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ABSTRACT

The teratogenic effect of the nootropic drugs Pyramem and Orocetam on the skeleton and internal organs of rats was investigated. Pregnant Wistar rats were treated orally by 200 mg/kg b. m. Pyramem and 200 mg/kg b. m. Orocetam during the period of organogenesis since the 7th until 15th day of pregnancy. The effect of these preparations on the fetuses in terms of malformations, skeletal fragility and abnormalities in the internal organs (lungs, liver, spleen and kidneys) close to delivery (day 20-21) was analyzed. The nootropics Orocetam and Pyramem failed to prove to be embryotoxic agents at all.

Key words: Orocetam, Pyramem, organogenesis, toxicity, rats

INTRODUCTION

Nootropics are a relatively new class of drugs developed actively in recent years in the hope that they will assist in the impaired nerve cell regeneration, enhance the intellectual and memory capacities as well strengthen the adaptive possibilities of the CNS towards extreme requirements because of their antioxidant effect (1).

This study aims at investigating the nootropic drugs "Pyramem" and "Orocetam" for their teratogenic effect and their skeletal and organ toxicity, in particular.

MATERIAL AND METHODS

The basic design of study is proposed from Sturman et al (3,4). The teratologic studies require application of the test agent when administered to the pregnant female animal during the period of organogenesis. Pregnant Lister Hooded rats (15 per group) were dosed by intraperitoneal application with Pyramem 200 mg/kg b. m., Orocetam 200 mg/kg b. m., and Aqua destillata 10 ml/kg b.m. during the period of organogenesis (days 7-15), taking day one when the female was found to be sperm positive.

Maternal body weights and food intake were monitored throughout the pregnancy since maternal toxicity adversely affects fetal development. Dams and fetuses were coded so that the researchers were unware of the dams' treatment schedules. Dams on day 21 of gestation were decapited after ether narcosis, weighed and the fetuses were removed by Caesarean section. Initially, the uterine horns on each side of the uterus checked externally. The number of implantations and reabsorptions (early or late absorptions) were noted and the number of fetuses counted. The number of corpus lutea in the ovaries were also counted to give an indication of the total number of fertilized eggs. The uteri were then opened. All pups, placentas and any late reabsorptions were placed on a plastic tray labelled in the order in which they were positioned in the uterus.

Fetuses selected for skeletal examination had their abdominal contents removed. They were weighed before examination for external abnormalities.

The livers were weighed in order to find out if drug treatment had exerted an effect on the liver of the fetus. Fetuses were skinned by placing in a water bath at 100° for 5 sec. Two methods were used for fetal examination of skeletal and visceral toxicity: the "Double staining" and the "Wilson section" method (2,4).

"Double staining" method for skeletal examination

Staining of the skeleton was made with 0,15 % of Alcian blue and 0,005 % of Alizarin red S. All the cartilages were stained blue but the ossified bones red. The entire fetal skeleton was examined and all the abnormalities, variations in degrees of ossification and lack of cartilage were recorded. Each bone was assessed for its size, shape, relative position and number of bones, and ribs and data were compared with the controls (Fig. 1).

Bouin's fixation for internal examination using the Wilson section method

Fetuses for visceral examination were processed using Bouin's solution to allow examination of the internal organs. This softened the tissues and decalcified the bones. After a minimum of 10 days cross sections were made.

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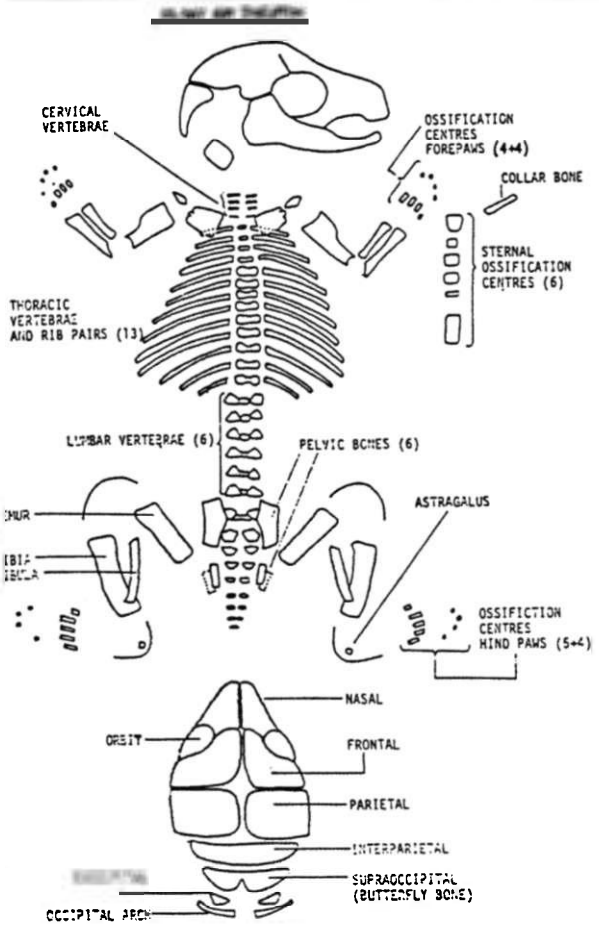

'ig. 1. Fetus examination after the method of double keleton staining for skeletal toxicity

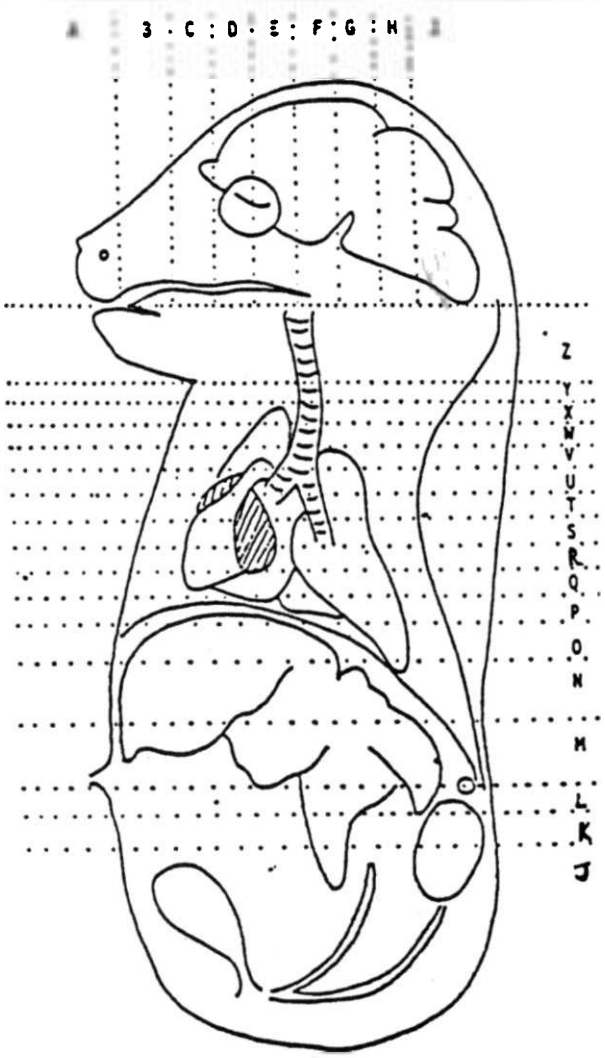

Fig. 2. Fetus examination after the Wilson section method for organic anomalies

'he sections should be 1 mm thin (18 sections of the head nd 20 of the body). Sections were then examined using a iicroscope to find out any abnormalities in the internal or- ans such as liver, lungs, kidneys and spleen (Fig. 2).)ata were statistically processed by using the variation nalysis and Student's *t*-test.

RESULTS AND DISCUSSION

Fetus weight and dimentions, liver and placenta weight /ere within the control values.

No abnormalities concerning the skeleton (head, trunk, and limbs) were detected. Skeletal fragility tests did not reveal any deviations from the controls (Table 1).

II. External examination of recent fetuses did not show any teratogenicity concerning the following signs:

'able 1. Mean rat fetal weights and lengths, and placenta and liver weights on 21 days of gestation

	Fetal weight (g)	Fetal length (mm)	Placenta weight (g)	Liver weight (g)	n
Controls	2,81 ± 0,24	33,48 ± 1,21	0,45 ± 0,07	0,2 ± 0,017	29
Pyramem	2,75 ± 0,29	34 ± 1,03	0,47 ± 0,09	0,19 ± 0,02	40
Orocetan	2,72 ± 0,28	33,69 ± 1,02	0,46 ± 0,08	0,18 ± 0,01	38
	p > 0,05	p > 0,05	p > 0,05	p > 0,05	

1. General appearance - external

a) Colour and weight of foetus

b) Major external anomalies such as: spina bifida; anencephaly; exencephaly; thinencephaly; cebocephaly.

c) Subcutaneous haemorrhages

2. Head: ears, eyes, nostrils, tongue, palate, and mouth

3. Limbs - fore, hind paws (number of digits, syndactyly, micromelia)

4. Rear end: anus, tail, ano-genital length: 2 mm for male and 1 mm for female.

The histomorphological examination using Bouins fixation for internal examination by the Wilson section method did not show any pathological changes of the internal organs such as lungs, liver, spleen, and kidneys.

CONCLUSIONS

The nootropic drugs studied did not demonstrate any evidence of embryotoxicity. In the animal groups treated with them, no abnormalities were observed in relation to the skeleton. The results from the investigations of the skeletal fragility and internal organ toxicity in the experimental animals treated with these two drugs did not differ from these of the healthy controls.

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